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Embedding Resveratrol-Loaded Lipid Nanoparticles and Hydroxyapatite into a Hydrophilic Peg-Based Matrix: Development of Hybrid Nanocomposite Mini-Tablets Suitable for Application in Extraction Sockets to Promote Tissue Healing

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Abstract : Tooth extraction often leads to inflammation, microbial infection, and alveolar bone resorption, thus requiring a comprehensive therapeutic approach. Resveratrol (RSV), a natural polyphenol known for its antioxidant, anti-inflammatory, and antimicrobial properties, could safely support tissue regeneration, but its clinical application is limited by its poor water solubility and low bioavailability following oral administration. Multicomponent lipid nanoparticles (mLNPs) can protect RSV, enhance its stability, and improve its interaction with the target tissue. The mLNP-RSV nanosystem, composed of Labrasol® (liquid lipid), glyceryl monostearate (solid lipid), menthol and glycyrrhetinic acid (functional excipients), which displayed synergistic antioxidant effect and wound repair activity. Based on these, the aim of this work was to propose an effective nano-based delivery system able to comprehensively improve the healing process after tooth extraction. To this scope, hydroxyapatite (HXA), a well-known safe and bioabsorbable bone substitute, was combined with mLNP-RSV. The first issue addressed in this work was the choice of an appropriate hydrophilic matrix capable of allowing mLNP-RSV freeze-drying in order to obtain a solid nanocomposite suitable for post-extraction socket insertion. Seven biocompatible polymers were then mixed in several weight ratios with the mLNP-RSV dispersion, subjected to freeze-drying, redispersed and evaluated by DLS analyses. SEM, XRD, FTIR, Raman spectroscopy and thermal analysis were used to extensively characterize and select the best nanocomposites. The latter were subjected to in vitro partitioning studies aimed at assessing their ability to release mLNP-RSV from the external hydrophilic matrix to lipophilic tissue. Finally, the optimal nanocomposite, mLNP-RSV-PEG10K, was combined with HXA to create a hybrid nanocomposite powder which was characterized in terms of bulk properties to assess its suitability as a pharmaceutical intermediate to further produce the final mini-tablet dosage form. The latter was obtained by direct compression of the hybrid powder and resulted compliant with the post-extraction socket cavity (≈59 mm^3) and thus potentially useful to facilitate localized delivery, promote healing and mitigate alveolar volume reduction. This system could ensure wound asepsis, support bone and soft tissue regeneration, and overcome RSV's pharmacokinetic limitations. By leveraging the combined properties of HXA and mLNP-RSV, the proposed hybrid nanocomposite mini-tablet represents an innovative therapeutic solution for effective and comprehensive post-extraction healing.

Keywords : hydroxyapatite, lipid nanoparticles, nanocomposite, resveratrol, wound healing.
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